Comment on Walker et al, page 3978

IL6 to the rescue

Peter E. Newburger  UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL

Granulocytes are produced in the bone marrow through a dynamic process (see figure) regulated by specific hematopoietic growth factors. Cytokines promoting the proliferation and differentiation of neutrophils include IL3, IL6, G-CSF, and GM-CSF (reviewed in Dinauer et al1), the last 2 of which serve as the primary regulators of granulopoiesis.

Accordingly, double-knockout G-CSF−/−/GM-CSF−/− mice show profound defects in neutrophil production and function.1 However, when challenged with microbial pathogens, these mice respond with increased production of both myeloid precursors and mature neutrophils, indicating an alternative pathway of "emergency" granulopoiesis.

In this issue of Blood, Walker and colleagues have identified IL6/sIL6R complexes as the mediators of this pathway in an in vitro model of emergency granulopoiesis in the absence of G-CSF and GM-CSF. In vivo experiments using triple-knockout G-CSF−/−/GM-CSF−/−/IL6−/− mice proved infeasible due to their poor viability. Therefore, the authors developed an in vitro culture system using colony formation from G-CSF−/−/GM-CSF−/− bone marrow as a bioassay for neutrophil-promoting activity in conditioned media from LPS-stimulated G-CSF−/−/GM-CSF−/− embryonic fibroblasts.

Previous studies had indicated essential roles for IL6 and, surprisingly, M-CSF for this activity, but neither was sufficient. The present work has elucidated a multicomponent pathway in which binding of IL6 to the soluble form of its receptor produces a transstimulatory IL6/sIL6R complex. The requirement for M-CSF may reflect its amplification of IL6 secretion or augmentation of sIL6R release by protease cleavage of membrane-bound IL6 receptor (mIL6R).

Pathways of homeostatic and emergency granulopoiesis. Top pathway: under normal conditions, G-CSF and GM-CSF regulate production of neutrophils by myeloid precursors in the bone marrow. During times of infection, the proposed emergency pathway is initiated by bacterial lipopolysaccharide (LPS) stimulation of tissue fibroblasts, stromal cells, and mononuclear phagocytes, resulting in the secretion of IL6 and M-CSF. The latter cytokine promotes cleavage of membrane IL6 receptor (mIL6R) to soluble sIL6R by ADAMs (a disintegrin and metalloproteases). The resultant soluble IL6/sIL6R complexes then circulate to the bone marrow, where they stimulate emergency granulopoiesis independent of G-CSF and GM-CSF.

The primary limitation of this work, as the authors acknowledge, is the in vitro model system that proved essential for identification of the neutrophil-promoting complex, but which lacked proof of in vivo applicability. Due to the redundancy of cytokine controls for neutrophil production, future studies may more easily demonstrate that IL6/sIL6R complexes are sufficient rather than that they are necessary for emergency granulopoiesis in vivo.

In the future, the physiological role of IL6/sIL6R complexes will undoubtedly be compared with that of IL6, the only form of the cytokine heretofore associated with hematopoiesis. IL6 directly binds to mIL6R, and the resultant multimer associates with the signal transduction protein gp130 (reviewed in Scheller et al3). mIL6R expression is limited to hepatocytes and some hematopoietic cells, but the ubiquitous expression of gp130, which also responds to IL6/sIL6R, renders nearly all cells potentially responsive to the IL6/sIL6R complex.

mIL6R has been detected in myeloid progenitor cells in vitro, and increases with their differentiation.3 If its expression is dependent upon G-CSF or GM-CSF, then IL6/sIL6R would provide a bypass mechanism unique to double-knockout cells. However, the soluble complex could also represent an independent physiological signal to myeloid precursors from tissue stromal and immune cells encountering microbial pathogens. The current study helps to solve the mystery of the neutrophil response in double-knockout mice. Further
Gas6 inflames cell interactions

Delphine Borgel  PARIS-SUD UNIVERSITY

Using Gas6–deficient mice, Tjwa and colleagues show that Gas6 plays a pivotal role in endothelial-cell response to inflammatory stimuli by promoting interaction of circulating cells with endothelium, amplifying local thrombosis, and increasing leukocyte infiltration into inflamed tissue.

Gas6, the product of growth-arrest–specific gene 6, is a member of the vitamin K–dependent protein family sharing significant homology with anticoagulant protein S, although it is devoid of anticoagulant properties. Gas6 is a ligand for 3 tyrosine kinase receptors (Axl, Tyro3, and Mer) whose signaling is implicated primarily in cell survival but also in cell proliferation, adhesion, and migration.1 Gas6 is also involved in platelet aggregation, as Gas6 knockout mice show impaired response to weak activation.2 The status of Gas6 as an antiapoptotic mediator in different cell types including endothelial cells is well established, but its role in endothelial-cell function has remained incompletely characterized.

In their study in this issue of Blood, Tjwa and colleagues explore the role of Gas6 in the interplay of cells implicated in the inflammatory response: endothelial cells, leukocytes, and platelets. They first report that when exposed to TNFα, endothelial cells lacking Gas6 show reduced expression of adhesion molecules (ICAM–1 and VCAM–1) and lowered cytokine release (IL1 and IL6). In keeping with these in vitro experiments, intravital microscopy observations show that upon activation, interaction between platelets, leukocytes, and endothelial cells is impaired in the absence of Gas6. This effect is related to a defect in P-selectin expression by activated endothelial cells.

Finally, using 3 different in vivo models of inflammation (endotoxemia, vasculitis, and heterotopic heart transplantation), Tjwa and colleagues note a decrease in leukocyte extravasation, inflammation, and thrombosis in Gas6-deficient animals. The diversity of in vivo experimental models of vascular injury used in this study reinforces the validity of its interesting results.

This newly identified function of Gas6 in vascular biology is very promising therapeutically, as it opens a new approach to treating pathologies in which endothelium inflammatory injury plays a pivotal role. Indeed, inhibition of the Gas6 pathway could be a new strategy in the treatment of sepsis, transplantation–induced organ rejection, or stroke—3 clinical situations in which endothelial protection could be beneficial and in which Gas6 has already been implicated.3–5 However, caution is needed, as differences between humans and mice have been reported concerning the Gas6 pathway. For example, Gas6 is present in mouse platelets, whereas no Gas6 was detected in human platelets.6 Only a few results regarding Gas6 involvement in human platelet aggregation have been published,7 suggesting some discrepancy between species.

Several aspects of Gas6 functions remain to be clarified. How does Gas6 promote responsiveness of endothelial cells to an inflammatory stimulus? This effect is not due to an increased release of Gas6 by activated endothelial cells. Furthermore, Gas6 is already present in the circulation and no activation process has been described so far that triggers the Gas6 pathway, which raises several questions. Are there any biochemical or structural differences between circulating Gas6 and Gas6 produced by endothelial cells that may explain the absence of constitutive Axl signaling by the circulating form? Is a cofactor, such as anionic phospholipid, required in Gas6 signaling? Is a local increase in Gas6 levels needed?

Nevertheless, the present study proposes a new role for Gas6 in vascular biology and provides a solid basis for future characterization of the implication of Gas6 in this field.

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REFERENCES

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